

iments in piglets demonstrated that TJqw2020 is a highly virulent strain. Our study suggests that recombination might be responsible for the varying pathogenicity of type 2 PRRSV strains, and highlights the importance of monitoring highly virulent recombinant PRRSV strains.

Declaration of Competing Interest

The authors have declared that no conflicts of interest.

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References

- Ye C., Wu X.P., Chen T.T., Huang Q.Y., Fang R.D., An T.Q. The updated analysis of African swine fever virus genomes: two novel genotypes are identified. *J Infect* 2020;**80**(2):232–54. doi:10.1016/j.jinf.2019.10.013.
- Li X.B., Xiao K.P., Zhang Z.P., Yang J.J., Wang R.C., Shen X.J., et al. The recombination hot spots and genetic diversity of the genomes of African swine fever viruses. *J Infect* 2020;**80**(1):121–42. doi:10.1016/j.jinf.2019.08.007.
- Lu G., Pan J.L., Zhang G.H. African swine fever virus in Asia: its rapid spread and potential threat to unaffected countries. *J Infect* 2020;**80**(3):350–71. doi:10.1016/j.jinf.2019.11.011.
- Eric J.N., James B.K., Colin D.J., John W.M., Eric J.B., Ann H.S., et al. Assessment of the economic impact of porcine reproductive and respiratory syndrome on swine production in the United States. *J Am Vet Med Assoc* 2005;**227**(3):385–92. doi:10.2460/javma.2005.227.385.
- Lunney J.K., Fang Y., Ladinig A., Chen N., Li Y., Rowland R.R., et al. Porcine reproductive and respiratory syndrome virus (PRRSV): pathogenesis and interaction with the immune system. *Annu Rev Anim Biosci* 2016;**4**:129–54. doi:10.1146/annurev-animal-022114-111025.
- Tian K., Yu X., Zhao T., Feng Y., Cao Z., Wang C., et al. Emergence of fatal PRRSV variants: unparalleled outbreaks of a typical PRRSV in China and molecular dissection of the unique hallmark. *PLoS ONE* 2007;**2**(6):e526. doi:10.1371/journal.pone.0000526.
- Zhou L., Wang Z.C., Ding Y.P., Ge X.N., Guo X., Yang H.C. NADC30-like strain of porcine reproductive and respiratory syndrome virus, China. *Emerg Infect Dis* 2015;**21**(12):2256–7. doi:10.3201/eid2112.150360.
- Zhang H., Guo X., Ge X., Chen Y., Sun Q., Yang H. Changes in the cellular proteins of pulmonary alveolar macrophage infected with porcine reproductive and respiratory syndrome virus by proteomics analysis. *J Proteome Res* 2009;**8**(6):3091–7. doi:10.1021/pr900002f.
- Zhao K., Ye C., Chang X.B., Jiang C.G., Wang S.J., Cai X.H., et al. Importation and recombination are responsible for the latest emergence of highly pathogenic porcine reproductive and respiratory syndrome virus in China. *J Virol* 2015;**89**(20):10712–16. doi:10.1128/JVI.01446-15.
- Ramos N., Mirazo S., Castro G., Arbiza J. Molecular analysis of porcine circovirus Type2 strains from Uruguay: evidence for natural occurring recombination. *Infect Genet Evol* 2013;**19**:23–31. doi:10.1016/j.meegid.2013.06.017.

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Infection-enhancing anti-SARS-CoV-2 antibodies recognize both the original Wuhan/D614G strain and Delta variants. A potential risk for mass vaccination?



Dear editor,

The aim of the present study was to evaluate the recognition of SARS-CoV-2 Delta variants by infection enhancing antibodies directed against the NTD. The antibody studied is 1052 (pdb file #7LAB) which has been isolated from a symptomatic Covid-19 patient¹. Molecular modeling simulations were performed as previously described². Two currently circulating Delta variants were investigated, with the following mutational patterns in the NTD :

- G142D/E154K (B.1.617.1)
- T19R/E156G/del157/del158/A222V (B.1.617.2)

Each mutational pattern was introduced in the original Wuhan/D614G strain, submitted to energy minimization, and then tested for antibody binding. The energy of interaction (ΔG) of the reference pdb file #7LAB (Wuhan/D614G strain) in the NTD region was estimated to -229 kJ/mol^{-1} . In the case of Delta variants, the energy of interaction was raised to -272 kJ/mol^{-1} (B.1.617.1) and -246 kJ/mol^{-1} (B.1.617.2). Thus, these infection enhancing antibodies not only still recognize Delta variants but even display a higher affinity for those variants than for the original SARS-CoV-2 strain.

The global structure of the trimeric spike of the B.1.617.1 variant in the cell-facing view is shown in Fig. 1A. As expected, the facilitating antibody bound to the NTD (in green) is located behind

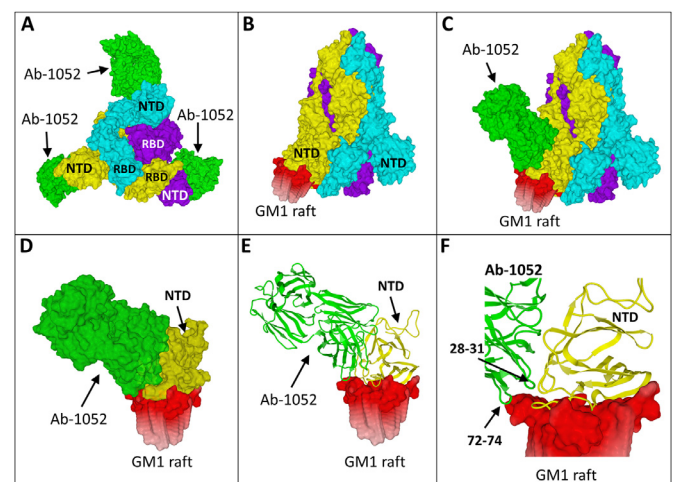


Fig. 1. Infection enhancing antibodies recognize the NTD of Delta variants. A. Molecular model of the Delta B.1.617.1 spike trimer as viewed from the host cell surface (chains A, B and C in cyan, yellow and purple, respectively), with the NTD and RBD of each chain indicated. The 1052 antibody is in green. B. Spike trimer with the B subunit bound to a lipid raft (with 6 ganglioside GM1 molecules). C. Trimolecular [spike-antibody-raft] complex. D. Focus on the NTD-antibody complex bound to the lipid raft. E. Secondary structures of the NTD (yellow) and the antibody (green) bound to lipid raft gangliosides. F. The 1052 antibody clamps the NTD and the edge of the lipid raft.

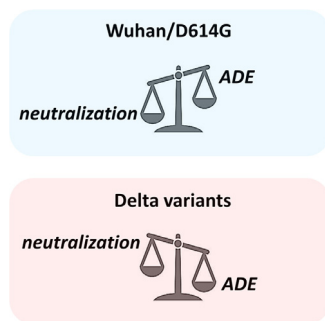


Fig. 2. Neutralization vs ADE balance according to SARS-CoV-2 strains.

the contact surface so that it does not interfere with virus-cell attachment. Indeed, a preformed antibody-NTD complex could perfectly bind to the host cell membrane. The interaction between the NTD and a lipid raft is shown in Fig. 1B, and a whole raft-spike-antibody complex in Fig. 1C. Interestingly, a small part of the antibody was found to interact with the lipid raft, as further illustrated in Figs. 1D–E. More precisely, two distinct loops of the heavy chain of the antibody encompassing amino acid residues 28–31 and 72–74, stabilize the complex through a direct interaction with the edge of the raft (Fig. 1F). Overall, the energy of interaction of the NTD-raft complex was raised from -399 kJ.mol^{-1} in absence of the antibody to -457 kJ.mol^{-1} with the antibody. By clamping the NTD and the lipid raft, the antibody reinforces the attachment of the spike protein to the cell surface and thus facilitates the conformational change of the RBD which is the next step of the virus infection process².

This notion of a dual NTD-raft recognition by an infection enhancing antibody may represent a new type of ADE that could be operative with other viruses. Incidentally, our data provide a mechanistic explanation of the FcR-independent enhancement of infection induced by anti-NTD antibodies¹. The model we propose, which links for the first time lipid rafts to ADE of SARS-CoV-2, is in line with previous data showing that intact lipid rafts are required for ADE of dengue virus infection³.

Neutralizing antibodies directed against the NTD have also been detected in Covid-19 patients^{4,5}. The 4A8 antibody is a major representative of such antibodies⁵. The epitope recognized by this antibody on the flat NTD surface is dramatically affected in the NTD of Delta variants², suggesting a significant loss of activity in vaccinated people exposed to Delta variants. More generally, it can be reasonably assumed that the balance between neutralizing and facilitating antibodies may greatly differ according to the virus strain (Fig. 2).

Current Covid-19 vaccines (either mRNA or viral vectors) are based on the original Wuhan spike sequence. Inasmuch as neutralizing antibodies overwhelm facilitating antibodies, ADE is not a concern. However, the emergence of SARS-CoV-2 variants may tip the scales in favor of infection enhancement. Our structural and modeling data suggest that it might be indeed the case for Delta variants.

In conclusion, ADE may occur in people receiving vaccines based on the original Wuhan strain spike sequence (either mRNA or viral vectors) and then exposed to a Delta variant. Although this potential risk has been cleverly anticipated before the massive use of Covid-19 vaccines⁶, the ability of SARS-CoV-2 antibodies to mediate infection enhancement in vivo has never been formally demonstrated. However, although the results obtained so far have been rather reassuring¹, to the best of our knowledge ADE of Delta variants has not been specifically assessed. Since our data indicate that Delta variants are especially well recognized by infection enhancing antibodies targeting the NTD, the possibility of ADE should

be further investigated as it may represent a potential risk for mass vaccination during the current Delta variant pandemic. In this respect, second generation vaccines⁷ with spike protein formulations lacking structurally-conserved ADE-related epitopes should be considered.

References

1. Li D., et al. In vitro and in vivo functions of SARS-CoV-2 infection-enhancing and neutralizing antibodies. *Cell* 2021;**184**:4203–19.
2. Fantini J., Yahi N., Azzaz F., Chahinian H.. Structural dynamics of SARS-CoV-2 variants: a health monitoring strategy for anticipating Covid-19 outbreaks. *J Infect* 2021;**83**:197–206.
3. Puerta-Guardo H., Mosso C., Medina F., Liprandi F., Ludert J.E., del Angel R.M.. Antibody-dependent enhancement of dengue virus infection in U937 cells requires cholesterol-rich membrane microdomains. *J Gen Virol* 2010;**91**:394–403.
4. Chi X., et al. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. *Science* 2020;**369**:650–5.
5. Liu L., et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. *Nature* 2020;**584**:450–6.
6. Iwasaki A., Yang Y.. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol* 2020;**20**:339–41.
7. Fantini J., Chahinian H., Yahi N. Leveraging coronavirus binding to gangliosides for innovative vaccine and therapeutic strategies against COVID-19. *Biochem Biophys Res Commun* 2021;**538**:132–6.

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Changes in the pathogenic spectrum of acute respiratory tract infections during the COVID-19 epidemic in Beijing, China: A large-scale active surveillance study



Dear editor,

Poole and colleagues demonstrated the impact of coronavirus disease 2019 (COVID-19) pandemic on the epidemiology of general respiratory viruses.¹ The prevalence of non-SARS-CoV-2 viruses during the COVID-19 epidemic has not been widely reported in China. We conducted to analyze the surveillance data of respiratory pathogens to explore the impact of public health measures against COVID-19 on the prevalence of non-SARS-CoV-2 pathogens in China.

Among 41,630 acute respiratory tract infections (ARTIs) between 01/02/2015 and 31/01/2021 in 35 hospitals from the Respiratory Pathogen Surveillance System (detailed in Supplemental materials), 37,490 (25,658 adults and 11,832 children) occurred before the COVID-19 epidemic (01/02/2015–31/01/2020), and 4140 (3379 adults and 761 children) occurred during the COVID-19 epidemic (01/02/2020–31/01/2021) (Fig. 1A–B).

All 41,630 cases were tested for 11 respiratory tract pathogens and 13,630 (32.74%, 95% CI 32.29% to 33.19%) had at least one positive result. Before the COVID-19 epidemic, the most common pathogen among the positive cases was influenza virus (IFV), followed by *Mycoplasma pneumoniae* (MP), human parainfluenza virus (HPIV), human rhinovirus (HRV), enterovirus (EV), respiratory syncytial virus (RSV), seasonal human coronavirus (HCoV), human